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10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-29,32-35 and 41-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-29,32-35 and 41-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10/13/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-13, 15-29, 32-35, 41-62 are pending and under consideration. Claims 14, 30-31, 36-40 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic goat comprising a bSP30a or a bSP30b promoter, wherein said promoter is operably linked to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said polypeptide is produced in said goat's saliva, does not reasonably provide enablement for a transgenic non-human mammal by way of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human mammal whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting 5' transcription control region ranging between about 4.6 KB- 30kB, wherein said polypeptide is produced in said mammal's saliva at a level of at least 0.5 mg/ml. Independent claim 20 is directed to a method, comprising: a)

providing; i) a transgenic non-human mammal whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting 5' transcriptional control region ranging between about 4.6 kB - 30 kB, said mammal capable of producing saliva, wherein said polypeptide is produced in said saliva and is collected from a salivary gland duct; ii) a flexible tubing to collect said saliva; b) making a surgical incision in said salivary gland duct; and c) cannulating said duct with said tubing. Independent claim 29 is directed to a method, comprising: a) providing; i) a first DNA sequence comprising 5' cis-acting expression signals, said first DNA sequence being derived from a first salivary gland secretory protein gene, said first gene ranging between about 4.6 kB - 30kB; ii) a second DNA sequence encoding a polypeptide of interest and a region encoding an operable secretion signal, said secretion signal being derived from a second salivary gland secretory protein gene; iii) a third DNA sequence comprising termination and 3' regulatory signals, said third DNA sequence being derived from a third salivary gland secretory protein gene, wherein said first, second, and third salivary gland secretory protein genes are not necessarily different; b) joining said first, second, third DNA sequences in operable linkage effective for salivary gland expression and saliva-specific expression of said polypeptide of interest to create a transgene construct; c) cloning said transgene construct to produce a vector; d) microinjecting said vector into a non-human mammalian embryo to produce a transgenic non-human mammal whose genome comprises a transgenic polypeptide transgene capable of engendering expression of said polypeptide in saliva of said non-human transgenic mammal, said non-human mammalian embryo is selected from the group consisting of porcine, bovine, ovine, caprine, and equine.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that

salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

The claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-Ips genes) (p 27-28) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of

salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229 (IDS)), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. The art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993 (IDS)). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims. Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with

respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Applicant's arguments are directed to the pertaining subject matter of the above rejection.

Applicants argue that claims 29 and 52 should be allowed because the bSP30a and bSP30b promoters are enabled. These arguments are partly persuasive for the generation of a transgenic goat with the particular the bSP30a and bSP30b promoters but applicants did not overcome the issues of unpredictability for the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims other than the bSP30a and bSP30b promoters in a goat. Applicants did not overcome the issue of unpredictability raised by the art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims in all transgenic non-human mammals with any or all different promoters and cis acting 5' transcriptional control Applicants by simply contemplating that using promoters that are ranging between about 4.6 kB-30 kB does not provide any guidance for any boundaries for designing the claimed salivary gland-specific transcription control region of ranging between about 4.6 kB- 30kB. An artisan will not be able to design specific salivary gland 5' flanking DNA required for salivary gland

specific expression without set sequence boundaries. Applicants have not disclosed what are the regulatory sequences necessary to achieve saliva specific expression and secretion of a polypeptide of interest in a transgenic mammal saliva at the claimed levels. Applicants have not correlated the use of parotid gland expression cassette, carrying all known regulatory regions in the Psp gene to the expression of a heterologous protein in the saliva of a transgenic mammal to overcome the art limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene as discussed by Samuelson. Applicants have not disclosed the main regulatory region or enhancer in the murine PSP gene to achieve the expression of a claimed polypeptide in a transgenic mammal. Note the specification recognizes the importance of regulatory sequences, in addition to the promoter sequences such as enhancers, splice signals, transcription termination signals and polyadenylation sites, among others which are useful regulatory sequences that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms." (see specification p 34). Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35). The

guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-lps genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva.

This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

To the extent the instant claims read on a transgenic non-human mammal with claimed characteristics or a method for creating said transgenic non-human mammal other than a transgenic goat comprising a bSP30a or a bSP30b promoter, wherein said promoter is operably linked to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said polypeptide is produced in said goat's saliva, the following rejection over the prior art is applicable.

Claims **1-28, 41-56** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mikkelsen et al**, (Nature 20(9): 2249-2255, 1992 (IDS)); **Laursen J and Hjorth J P,** (Gene 198(1-2): 367-72, 1997) in view of **Golovan et al, Nat Biotechnol, 19(5):429-33, 2001; Golovan et al., (Nat Biotechnol, 19(8):741-5, 2001); Swenson and Reece** (In: Dukes' Physiology of Domestic Animals, 11th Edition., Comstock Publishing Assoc. Ithaca, NY. pp 399-400, 1993); **Lubon et al,** (Transfusion Medicine Reviews X(2): 131-141, 1996); **Lubon et al,** (US. 5,880,327(IDS)); **Coppes et al,** (Radiation Research, 153: 339-346, 2000 (IDS)).

Mikkelsen et al, (Nature 20(9): 2249-2255, 1992), teach transgenic animals (mice) by using a Lama DNA construct with the parotid secretory protein (PSP) mini gene directing the expression of a heterologous cDNA encoding the C-terminal peptide of human factor VIII to salivary glands and the secretion of the human factor VIII into saliva (abstract). Mikkelsen teaches in the Lama construct the regulatory region included **4.6 kb of 5' flanking sequence** sufficient to direct human factor VIII trasngene expression to the salivary glands (abstract). Mikkelsen suggests the existence of a parotid specific enhancer for the PSP gene which is not included in the Lama construct, and there is a searching for this putative enhancer (p 2254, 1st column, last paragraph). Mikkelsen suggests that sequences located at a considerable distance from the mini gene are required for parotid specific expression (p 2254, 2nd column, 2nd paragraph). Mikkelsen suggests salivary gland expression of the Lama/FVIII-C hybrid gene and the demonstrated secretion of the encoded peptide into saliva it promotes a model for the salivary glands as useful for experimental model systems for investigations such as testing and optimizing transgene constructs for secretion of proteins, analysis of secondary modifications of heterologous synthesized proteins expressed in salivary glands, and finally as a unique possibility to study the effects of altered composition of saliva on for instance digestion and uptake of foodstuffs in transgenic animals. **Laursen J and Hjorth J P,** (Gene 198(1-2): 367-72,

1997) teaches the Psp mini gene for the generation of transgenic mice for the secretion of human blood coagulation factor VIII light chain in the saliva of transgenic mice in a study of the salivary glands as bioreactors (p 367, 2nd column bridge to p 368). Laursen teaches Tg mice with high-level parotid gland expression using a Lama II construct with a 25-Kb DNA fragment (PspX25) carrying the entire structural part of the Psp gene and large flanking areas (p 368, 1st column, 1st paragraph). Laursen J and Hjorth J P, teach the trasngene expression at high levels specifically in the parotid glands (p 370, 2nd column, 2nd paragraph and Table I). Laursen J and Hjorth J P teach Tg1356 expressed the endogenous Psp mRNA at relatively low levels in the sublingual glands (Fig. 3C). This mouse carried both of the two known alleles of the cassette. Psp gene and as one of these alleles (Psp^a) lacks expression in the sublingual glands it seems likely that this is at least partly **a *cis*-effect** (p 370, 2nd column, 2nd paragraph). Laursen J and Hjorth J P teach a comparison of Lama (Mikkelsen construct) and Lama II indicates that high-level expression of the Psp gene in the parotid glands is depended on regulatory elements that are situated between -11.5 and -6.5 Kb and/or between -8.3 Kb and +10.9 Kb (p 371, 1st column). The addition of these sequences to the Lama construct resulted in an approximately 40-fold enhancement of parotid gland expression (p 371, 1st column). Swenson and Reece and Laursen J and Hjorth J P, differ from the present invention for not teaching a porcine, ovine, bovine and equine.

However, at the time of the instant invention, **Golovan et al, (Nat Biotechnol, 19(5):429-33, 2001); and Golovan et al., (Nat Biotechnol, 19(8):741-5, 2001)** teach bacterial phytase is expressed in the parotid and submandibular glands of transgenic mice and pigs using the R15-PRP and PSP promoters and phytase was detected in mouse saliva at concentrations of 15 ug/ml, for the respective constructs. Golovan et al., Nat Biotechnol. 19(8):741-5 (2001) teach the presence of phytase in the parotid and submandibular glands

transgenic mice and pigs using the R15-PRP and PSP promoters is essential for binding to amino acids and starch and prevent their digestion and adsorption and pigs producing phytase in the saliva present a new biological approach for reducing phosphorus pollution (p 744, 2nd column). Golovan et al., Nat Biotechnol. 19(5):429-33 (2001); and Golovan et al., Nat Biotechnol. 19(8):741-5 (2001) teach that salivary glands can be used for efficient production of other heterologous proteins (p 432, 1st column. 1st paragraph). Animals of both sexes start producing saliva early and do so throughout their life. Pigs, for example, can produce an average 15 L of saliva per day containing an average protein concentration of 4 mg/ml (60 g protein per day) (p 432, 1st column. 1st paragraph). At the 1% level, this translates into 0.6 g/day or 219 g/year/pig of heterologous proteins (p 744, 2nd column). **Swenson and Reece** teach ruminants produce a high daily output of saliva (6 to 16 L/d in sheep; 60 to 160 L/d in cattle) (p 399-400). Swenson and Reece teach the parotid glands produce about one half of the daily salivary output, which is serous, isotonic, and strongly buffered, in contrast to submaxillary, sublingual and labial glands which produce small quantities of mucous, hypotonic and weakly buffered saliva (p 399-400, see table 21.2 salivary glands and their properties in sheep). **Lubon et al,** (Transfusion Medicine Reviews X(2): 131-141, 1996) supplements the teachings of Golovan/ Swenson and Reece by teachings a wide variety of genes have been expressed in a wide variety of transgenic animals (rabbits, sheep, pigs, and goats) and a variety of blood proteins and therapeutic proteins secreted in body transgenic animal body fluids and milk (whole document)including factor VIII with the cDNA sequence for the regulatory region for m parotid secretory protein secreted in saliva (p 133, Table 1). **Lubon et al,** (US. 5,880,327) teach a mouse expressing human prothrombin and F8 under the control of the WAP promoter, where the mouse produces detectable quantities prothrombin in its saliva (column 5, lines 13-18). As such, Golovan taken with Swenson and Reece taken with Lubon provide sufficient

motivation for one of ordinary skill in the art to apply the Lama II construct of Laursen J and Hjorth J P, for phytase or a therapeutic transgene production in the parotid glands of a transgenic animal. **Coppes et al,** (Radiation Research, 153: 339-346, 2000) teaches that it is routine in the art to use the insertion of a duct cannula made from Medical Grade Silicone Tubing inserted into the parotid glands of rats after a small incision (p 340).

Accordingly, in view of the teachings of Golovan taken with Swenson and Reece, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the Lama II construct of Laursen J and Hjorth J P by adding of a phytase transgene in a transgenic pig with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to produce large quantites of human blood coagulation factor VIII light chain in the saliva as taught by the physiological role of a gene of interest by the generation of a knockout mouse as taught by Laursen J and Hjorth J P, and particularly since of Laursen J and Hjorth J P, suggest the addition of the cis-element sequences to the Lama construct resulted in an approximately 40-fold enhancement of parotid gland expression. One of ordinary skill in the art would have been sufficiently motivated to make such a modification a modification since Swenson and Reece teach parotid glands produce about one half of the daily salivary output, which is serous, isotonic, and strongly buffered, in contrast to submaxillary, sublingual and labial glands which produce small quantities of mucous, hypotonic and weakly buffered saliva and particularly since Lubon teaches production of large quantities of therapeutic proteins in the milk of transgenic animals a bioreactors poses limitations with respect to transgene inheritance and stability, appropriate posttranslational modifications on heterologous proteins, industrial production procedures, and long term effects of foreign protein expression on transgenic animal bioreactor (p 131, 2nd column 1st paragraph). One of ordinary skill in the art would have been

sufficiently motivated to make such a modification a modification since Laursen J and Hjorth J P, teach the Lama II construct results in the long term transgene expression in the saliva in order to solve the limitation of posttranslational modifications on heterologous proteins as taught by Lubon and since Swenson and Reece teach parotid glands produce salivary output, which is serous, isotonic, and strongly buffered. Lubon (US. 5,880,327) offers motivation for using mammals producing large volumes of body fluids in stating an important need remains for an efficient and relatively inexpensive means of producing large quantities of infectious-free, human factor VIII protein suitable for clinical use (column 2, lines 35-37). Lubon offers motivation since the transgenic animal system they described produces human factor VIII protein recombinant satisfies this need and since Golovan teach the antibacterial properties of phytase in saliva. In addition, one of ordinary skill in the art would have been sufficiently motivated to use the insertion of a duct cannula in the salivary gland for the collection of saliva as taught by Coppes. Thus, at the time of the claimed invention it would have been obvious to the skilled artisan to make a cow, expressing prothrombin in its salivary gland using the tubing technology of Coppes each of which produces large volumes of saliva than mice given the teachings of Lubon in view of the combined cited references.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claims **29, 32-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikkelsen et al, (Nature 20(9): 2249-2255, 1992); Laursen J and Hjorth J P, (Gene 198(1-2): 367-72, 1997) in view of Golovan et al, Nat Biotechnol, 19(5):429-33, 2001; Golovan et al., (Nat Biotechnol, 19(8):741-5, 2001); Swenson and Reece (In: Dukes' Physiology of Domestic Animals, 11th Edition., Comstock Publishing Assoc. Ithaca, NY. pp 399-400, 1993); Lubon et al, (Transfusion Medicine Reviews X(2): 131-141, 1996); Lubon et al, (US. 5,880,327); Coppes et

al, (Radiation Research, 153: 339-346, 2000) and further in view of **Deboer et al** (6,140,552 (IDS)).

The teachings of Mikkelsen/Laursen J and Hjorth J P/Golovan/Golovan/ (Nat Biotechnol, 19(8):741-5, 2001)/Swenson and Reece/Lubon et al, (Transfusion Medicine Reviews X (2): 131-141, 1996)/Lubon et al, (US. 5,880,327)/Coppes apply here as indicted above.

The above sited combined references do not teach i) a first DNA sequence comprising 5' cis-acting expression signals, said first DNA sequence being derived from a first salivary gland secretory protein gene, said first gene ranging between about 4.6 kB - 30kB; ii) a second DNA sequence encoding a polypeptide of interest and a region encoding an operable secretion signal, said secretion signal being derived from a second salivary gland secretory protein gene; iii) a third DNA sequence comprising termination and 3' regulatory signals, said third DNA sequence being derived from a third salivary gland secretory protein gene, wherein said first, second, and third salivary gland secretory protein genes are not necessarily different; b) joining said first, second, third DNA sequences in operable linkage effective for salivary gland expression and saliva-specific expression of said polypeptide of interest to create a transgene construct; c) cloning said transgene construct to produce a vector; d) microinjecting said vector into a non-human mammalian embryo to produce a transgenic non-human mammal whose genome comprises a transgenic polypeptide transgene capable of engendering expression of said polypeptide in saliva of said non-human transgenic mammal, said non-human mammalian embryo is selected from the group consisting of porcine, bovine, ovine, caprine, and equine.

However, at the time of the instant invention Deboer et al teach a method with the claimed elements of the instant invention using transgenes encoding human lactoferrin, human serum albumin and human Protein C in conjunction with a .alpha.S1 casein secretory signal

sequence under control of .alpha.S1 casein expression regulation sequences are designed to produce and secrete these heterologous polypeptides from the mammary gland of a lactating transgenic mammal into its milk and saliva (see column 91-92). Deboer et al teach the animal showed an hLF expression in saliva of 100 ng/ml and not at 5.0 mg /ml as in the instant invention.

Accordingly in view of the teachings of Mikkelsen/Laursen J and Hjorth J P/Golovan/Golovan/(Nat Biotechnol, 19(8):741-5, 2001)/Swenson and Reece/Lubon et al, (Transfusion Medicine Reviews X(2): 131-141, 1996)/Lubon et al, (US. 5,880,327)/Coppes one of ordinary of skill in the art would have been motivated to use the system of the Mikkelsen/Laursen J and Hjorth J P/Golovan/Golovan/(Nat Biotechnol, 19(8):741-5, 2001)/Swenson and Reece/Lubon et al, (Transfusion Medicine Reviews X(2): 131-141, 1996)/Lubon et al, (US. 5,880,327)/Coppes in order o increase the production of therapeutic transgenes in transgenic porcine, bovine, ovine, carpine and equine as bioreactors at the claimed concentrations.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
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